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Defying age: myth or reality?

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Defying age: myth or reality?

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In this issue of *Haematologica*, Kawamura and others from Japan report on donor selection for allogeneic hematopoietic cell transplant in adults with hematologic malignancy.[1] They observed superior survival after transplantation of grafts from HLA-matched unrelated donors aged <50 years compared to matched siblings in patients aged ≥50 years. Compared to matched sibling transplantation, in patients aged ≥50 years, a survival advantage was not observed with older HLA-matched unrelated donors. In younger patients, survival did not differ after transplantation of grafts from HLA-matched unrelated donors and matched sibling transplantation. This report concluded with a donor selection algorithm based on the age of the patient. For patients aged <50 years, a matched sibling remains the donor of choice followed in descending order: i) HLA-matched unrelated donors regardless of age, ii) 1-HLA locus mismatched related or unrelated donors or umbilical cord blood and iii) ≥2-HLA loci mismatched

related donors. On the other hand, for older patients, an HLA-matched unrelated donor aged <50 years is the donor of choice followed in descending order: i) matched sibling, ii) HLA-matched unrelated donor aged ≥50 years or a younger 1-HLA locus mismatched unrelated donor, iii) 1-HLA locus mismatched related or 1-HLA locus mismatched older unrelated donor or umbilical cord blood and iv) ≥2-HLA loci mismatched related donors.

Worldwide an increasing proportion of people are over the age of 65 years and in Japan they account for approximately 29% of the population forcing a need to address the needs of a growing population. Selection of unrelated donors for hematopoietic cell transplantation has evolved such that HLA-matching at HLA-C locus, allele-level HLA-matching including for selecting umbilical cord blood units (after ensuring a minimum total nucleated cell dose per kilogram patient body weight)[2,3] have contributed to better survival after unrelated donor transplantation. An earlier report from the United States showed that for every 10-year increment in donor age, there is a 5.5% increase in the hazard ratio for overall mortality.[4] The World Marrow Donor Association (WMDA; www.wmda.org) an international body that was established in 1994 provides a global platform to improve access to hematopoietic cell transplantation. The WMDA's standards recommend unrelated donors must be aged 18 – 60 years with the option for unrelated donor registries to determine lower and upper donor age in regard to registration and donation for their respective registries. In Japan, unrelated donors may join the registry aged 18 years and donate beginning at 20 years and up to their 55th birthday.

How can the findings of Kawamura et al inform changes with respect to the upper age limit for unrelated adult donors for donation, and donor selection applying evidenced-

based data towards a revised donor selection algorithm? First, based on the findings of Kawamura et al should the upper age limit for donation be lowered to a donor's 50th birthday? Their report suggests that in Japan the median age at transplantation is the 6th decade. The report does not provide information on the demographics of the Japanese donor registry or the median age of donors selected through the registry. Nevertheless, consideration for revising existing guidelines for the donor registry will be influenced by real world donor selection practice in Japan and available HLA haplotypes in the Japanese donor registry. Retaining donors with uncommon HLA haplotypes through their 55th birthday expands the donor pool whereas retaining donors with common HLA haplotypes beyond their 50th birthday is unlikely to be beneficial considering the potential benefit of selecting younger donors' other prognostic factors being equal.

Second, although the donor selection algorithm proposed by Kawamura et al is evidenced-based some of its recommendations may be limited in its applicability worldwide. There is agreement that younger adult unrelated and mismatched related donors improve survival.[5,6] Consequently, the practice of selecting a young HLA-matched unrelated donor instead of an older matched sibling may be acceptable worldwide. With the inclusion of high dose post-transplant cyclophosphamide to the transplant-regimen, survival has improved after transplantation of grafts from ≥2-HLA loci mismatched related and 1-HLA locus mismatched unrelated donor transplantations to an extent that transplant-outcomes are comparable to that after matched sibling transplantations.[7,8] The use of umbilical cord blood as a graft has decreased substantially in recent years to an extent it accounts for approximately 1% of allogeneic

transplants.[9] Ready availability of banked umbilical cord blood units was an advantage in past years when transplantation was needed urgently. However, with enhancements to donor search strategy offered through the unrelated donor registries the likelihood of identifying a fully matched unrelated donor (matched at the allele-level at HLA-A, -B, -C, -DRB1) is more readily apparent and offers an opportunity to proceed directly to an alternative donor without a prolonged search for an matched unrelated donor and without significant survival differences across the donor types although the 2-year survival ranged between 60% to 70%.[10]

What have we learned? The findings of Kawamura et al and others have shown that selecting a young donor when available offer a survival advantage and must be incorporated into clinical practice. Most transplant centers would still choose an HLA-matched related or HLA-matched unrelated donor as their first choice. The choice of an alternative donor (i.e., HLA-mismatched related or unrelated donor or umbilical cord blood) will depend on center experience and opportunities to enroll to clinical trials testing novel strategies aimed at improving one or more transplant-outcomes. More studies comparing alternative donor types are needed to advance knowledge as most patients now-a-days are likely to have a choice of donors other than a matched sibling. In this context, a simplified donor selection algorithm is proposed for consideration with an understanding that this will be revised as future studies yield more knowledge regarding alternative donor selection (Figure 1). While the majority of allogeneic transplantations are for hematologic malignancy and most data available have relied on studying hematologic malignancy, there is a need to study donor selection for non-malignant hematologic diseases.

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Figure Legend

Simplified donor selection algorithm

Simplified Donor Selection Algorithm